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Health and Environmental Effects Profile for 4-Chloro-2-Methylaniline and 4-Chloro-2-Methylaniline Hydrochloride

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16. ABSTRACT

The Health and Environmental Effects Profile for 4-chloro-2-methylaniline and 4-chloro-2-methylaniline hydrochloride was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 4-Chloro-2-methylaniline and 4-chloro-2-methylaniline hydrochloride have been evaluated as carcinogens. The human carcinogen potency factors (q_1^*) for 4-chloro-2-methylaniline and 4-chloro-2-methylaniline hydrochloride are 5.8×10^{-1} and 4.6×10^{-1} $(mg/kg/day)^{-1}$, respectively, for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 4-chloro-2-methylaniline and 4-chloro-2-methylaniline hydrochloride is 5000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR 4-CHLORO-2-METHYLANILINE AND 4-CHLORO-2-METHYLANILINE HYDROCHLORIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

Commercial 4-chloro-2-methylaniline is a crystalline, grayish white solid at ambient temperatures. It is sparingly soluble in water, but is soluble in ethanol and dilute acids (Hawley, 1981; Weast, 1980). The hydrochloride can be assumed to be soluble in water since the parent chemical is soluble in dilute acid (Hawley, 1981). As of January 1985, only Pfister Chemical Inc., Ridgefield, NJ, manufactured 4-chloro-2-methylaniline in the United States, but its recent production volume is not available (SRI, 1985). In 1983, 44,147 pounds of 4-chloro-2-methylaniline and its hydrochloride was imported in the United States (USITC, 1984). According to the available literature, there is no indication that the hydrochloride is currently manufactured in the United States (USITC, 1984). 4-Chloro-2-methylaniline is prepared by the acetylation of o-toluidine, chlorination of acetyl product and subsequent saponification of the chlorinated product (Hawley, 1981; Catino and Farris, 1978). 4-Chloro-2-methylaniline and its chloride are used for the production of azo dyes. The free base, 4-chloro-2-methylaniline, is also used as an intermediate for the production of pigments and chlordimeform, an insecticide and acaricide (IARC, 1978).

Adequate data are not available in the literature to assess the environmental fate and transport of 4-chloro-2-methylaniline or its hydrochloride. The conclusions reached regarding the fate and transport of this chemical in different media are based on experimental data for this chemical and data for chemically similar compounds. Based on the photolysis experiment of Knowles and Gupta (1969), it has been concluded that direct photolysis may be a significant fate process for this chemical in water, although no half-life from this reaction can be derived. The biodegradation study

results of Matsui et al. (1975) indicate that 4-chloro-2-methylaniline will undergo biotransformation in water, but the quantitative significance of this process in determining the overall fate of 4-chloro-2-methylaniline in water cannot be evaluated. Based on the soil study by Bollag et al. (1978), it has been concluded that sorption may be a significant process in water. The volatilization of this chemical from water may not be significant in water containing humic materials in suspended particulates.

In air, the reaction of this chemical with OH radical may be the fate-determining process. Based on the rate constant for OH radical reaction with a similar compound (Atkinson, 1985), the estimated half-life of this reaction is ~3 hours.

Biodegradation may be an important fate-determining process for this chemical in soil. Bollag et al. (1978) reported only 2% of the compound volatilized in 40 days from a soil containing 3.4% organic matter. The binding of the chemical in soil was strong; of the total amount of the compound applied to a soil containing 3.4% organic matter, ~61.7% of the residue remained irreversibly sorbed to soil after 42 days. Therefore, significant leaching of this material from most soils is unlikely, although leaching may occur in sandy soils and in soils from waste disposal and spillage sites.

4-Chloro-2-methylaniline or its hydrochloride has apparently never been detected in water, air or foods.

There was no information available concerning the toxicity of 4-chloro-2-methylaniline or its hydrochloride to aquatic organisms. 4-Chloro-2-methylaniline was one of the principal metabolites formed by the algae Chlorella sp. and Oscillatoria sp. exposed to chlordimeform or 4-chloro-o-formotoluidide (Benezet and Knowles, 1981).

4-Chloro-2-methylaniline and its hydrochloride appear to be substantially absorbed from the gastrointestinal tract and widely distributed to tissues of rats. The distribution of the two compounds appears to be similar. Knowles and Gupta (1970) reported that the highest levels of radioactivity 72 hours after an unspecified oral dose of 4-chloro-2-[methyl^{14}C]-aniline to male and female Sprague-Dawley rats were found in the fat, liver and kidneys. Hill et al. (1979) reported that irreversible binding of radioactivity to macromolecules was greatest in the liver of Osborne-Mendel rats treated intraperitoneally with 4-chloro-2-[methyl^{14}C]-aniline hydrochloride.

The metabolism of 4-chloro-2-methylaniline and its hydrochloride has been studied *in vivo* and *in vitro*, respectively. These studies suggest that only 4-chloro-2-methylaniline hydrochloride has been tested for carcinogenicity. In an NCI (1978) bioassay, no increased incidences of tumors occurred in male or female Fischer 344 rats fed 1250 or 5000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet for 107 weeks. The incidence of hemangiosarcomas was significantly increased in males treated at 3750 and 15,000 ppm and in female mice treated at 1250 or 5000 ppm for 92-99 weeks relative to controls. In another study, no increase in tumor incidence was reported in male rats treated at dietary levels of 750 or 1500 ppm compared with controls (Weisburger et al., 1978). Male mice treated at 750 or 1500 ppm and female mice treated at 2000 or 4000 ppm, however, had a significant dose-related increase in incidence of vascular hemangiosarcomas and hemangiomas relative to controls.

4-Chloro-2-methylaniline did not induce reverse mutations in several tested strains of *Salmonella typhimurium* or in *Escherichia coli* with or without S-9 activation (Rashid et al., 1984); however, the compound

inhibited growth of DNA repair-deficient strains of S. typhimurium and E. coli (Rashid et al., 1984). 4-Chloro-2-methylaniline induced DNA damage in Chinese hamster lung fibroblasts (Zimmer et al., 1980) and inhibited cell growth and RNA synthesis in HeLa cells (Murakami and Fukami, 1974). Positive results have also been reported for inhibition of testicular DNA synthesis in male mice (Seiler, 1977) and for mutations at recessive gene coat color loci in mice (Lang, 1984).

4-Chloro-2-methylaniline hydrochloride produced negative results for mutations in most S. typhimurium strains, with or without S-9 addition (Zimmer et al., 1980; Haworth et al., 1983), but equivocal results were found in strain TA100. Negative results were reported in the heritable translocation assay (Lang and Adler, 1982).

Fertility of male NMRI/SPF mice was not affected following oral treatment with 200 mg/kg/day 4-chloro-2-methylaniline hydrochloride (Lang and Adler, 1982). No differences in number or viability were found in litters of female C57BL/6J mice treated by gavage with 100 mg/kg of the compound on days 8, 9 and 10 of pregnancy (Lang, 1984). Pertinent data regarding the teratogenicity of 4-chloro-2-methylaniline or its hydrochloride salt were not available.

Subchronic studies of 4-chloro-2-methylaniline hydrochloride showed no effect on survival but a slight but not dose-related decrease in body weight in male Fischer rats fed 250-10,000 ppm in the diet for 7 weeks (NCI, 1978). Splenomegaly was noted in males at doses $\geq$6500 ppm. At doses $\geq$6200 ppm, a dose-related decrease in body weight occurred in female rats administered the compound in the diet for 7 weeks. In the female rats, 100% mortality occurred at 50,000 ppm. Male mice showed a slight but not dose-related decrease in body weight, but no mortality after 7 weeks of treatment with 2000-15,000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet (NCI,

1978). At concentrations of 15,000-20,000 ppm, no mortality occurred in female mice, but body weight was decreased by 10-20% after 7 weeks.

Chronic toxicity data from the NCI (1978) bioassay showed a slight decrease in body weight of high-dose (5000 ppm) male and female rats relative to controls after 30 weeks of treatment with 4-chloro-2-methylaniline hydrochloride in the diet. Survival of both dose groups of female mice (1250 and 5000 ppm) and high-dose male mice (15,000 ppm) was decreased after 60 weeks of treatment. The high mortality was secondary to tumor development. Mean body weights of both sexes of mice showed a dose-related decrease throughout the bioassay. Kidney hemosiderosis was apparent in both sexes of mice but was related to tumor development.

Irritation of the bladder has been reported in 11 workers involved in the manufacture of 4-chloro-2-methylaniline (Currie, 1933) and in cats treated subcutaneously with the compound (Kimbrough, 1980). The intraperitoneal LD_{50} for mice was 680-720 mg/kg and 560-700 mg/kg for rats (Weisburger et al., 1978). 4-Chloro-2-methylaniline inhibited rat brain monoamine oxidase *in vitro* (Benezet and Knowles, 1976).

4-chloro-2-methylaniline and its hydrochloride are metabolized by hepatic P-450 enzymes. Based on metabolites identified in various studies, it has been suggested that 4-chloro-2-methylaniline is oxidized to 5-chloroanthranilic acid and 5-chloro-2-hydroxylaminotoluene, acetylated to 4-chloro-2-methylacetanilide and condensed to form 4,4'-dichloro-2,2'-dimethylazobenzene (Knowles and Gupta, 1970; Hill et al., 1979).

Knowles and Gupta (1970) reported that 4-chloro-2-methylaniline and its metabolites were excreted in the urine and feces. Of the radioactivity of an unspecified oral dose of the radiolabeled parent compound, 71% was eliminated in the urine and 24.5% was eliminated in feces within 72 hours of administration.

Based on the data for increased incidences of hemangiosarcoma/hemangioma in female mice in the Weisburger et al. (1978) study, q_1*s of 4.6×10^{-1} $(mg/kg/day)^{-1}$ for 4-chloro-2-methylaniline hydrochloride and 5.8×10^{-1} $(mg/kg/day)^{-1}$ for 4-chloro-2-methylaniline were derived. The water concentrations associated with increased lifetime risks at levels of 10^{-5}, 10^{-6} and 10^{-7} are 7.6×10^{-4}, 7.6×10^{-5} and 7.6×10^{-6} mg/ℓ for 4-chloro-2-methylaniline hydrochloride and 6.0×10^{-4}, 6.0×10^{-5} and 6.0×10^{-6} for 4-chloro-2-methylaniline, assuming that a 70 kg man consumes 2 ℓ water/day. F factors of 2.5 $(mg/kg/day)^{-1}$ for 4-chloro-2-methylaniline hydrochloride and 3.1 $(mg/kg/day)^{-1}$ for 4-chloro-2-methylaniline were also derived from the female mice data in the Weisburger et al. (1978) study. Because the F factors were >1, these are Potency Group 2 chemicals. Because data for carcinogenicity in animals are sufficient and in humans are inadequate, these chemicals are classified in EPA Group B2, probable human carcinogens. Potency Group 2 chemicals in EPA Group B2 have a MEDIUM hazard ranking under CERCLA.

RQs of 5000 were derived for these chemicals based on reduced body weight gain in female mice in the NCI (1978) study.

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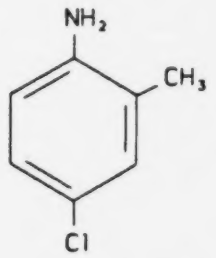
LIST OF ABBREVIATIONS

CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
ID_{50}	Dose needed to inhibit cell growth by 50%
K_{ow}	Octanol/water partition coefficient
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effect dose
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
ppm	Parts per million
RNA	Ribonucleic acid
RV_e	Effect-rating value
RV_d	Dose-rating value
TLC	Thin layer chromatography
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

1.1.1. **4-Chloro-2-methylaniline.** 4-Chloro-2-methylaniline is also called benzenamine, 4-chloro-2-methyl; p-chloro-o-toluidine; azoic diazo component 11, base; 2-amino-5-chlorotoluene; and 5-chloro-2-aminotoluene (U.S. EPA, 1986a). The structure, empirical formula, molecular weight and CAS Registry number of this chemical are as follows:

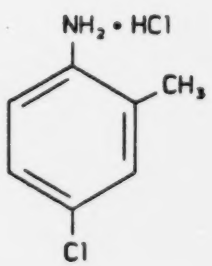


Empirical formula: C_7H_8ClN

Molecular weight: 141.61

CAS Registry number: 95-69-2

1.1.2. **4-Chloro-2-methylaniline Hydrochloride.** 4-Chloro-2-methylaniline hydrochloride is also called benzenamine, 4-chloro-2-methyl, hydrochloride; o-toluidine, 4-chloro-, hydrochloride; p-chloro-o-toluidine, hydrochloride; azoic diazo component 11; 2-amino-5-chlorotoluene, hydrochloride; and 5-chloro-2-aminotoluene, hydrochloride (U.S. EPA, 1986a). The structure, empirical formula, molecular weight and CAS Registry number for the hydrochloride are as follows:



Empirical formula: $C_7H_9Cl_2N$

Molecular weight: 178.1

CAS Registry number: 3165-93-3

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Commercial 4-chloro-2-methylaniline is a crystalline, grayish white solid at ambient temperature. It is sparingly soluble in water, but is soluble in ethanol and dilute acids (Hawley, 1981; Weast, 1980). Other available physical properties of this compound are listed below:

Melting point:	29-30°C	Weast, 1980
Boiling point:	241°C	Weast, 1980
Water solubility:	64 mg/ℓ (estimated from log K_{ow} and the correlation equation log S - 0.922 log K_{ow} + 4.184)	Lyman et al., 1982
Log K_{ow}:	2.58 (estimated from Leo's fragmentation method by computerized CLOGP routine)	U.S. EPA, 1986b
Flash point:	99°C	Aldrich, 1986

Data on the physical properties of the hydrochloride salt could not be located in the available literature as cited in the Appendix. Since its parent chemical is soluble in dilute acids (Hawley, 1981), the hydrochloride can be assumed to be soluble in water.

Chemically, the amino group of both 4-chloro-2-methylaniline and its hydrochloride salt can be diazotized, and the diazotization and the subsequent condensation reaction is commercially useful for the preparation of several dyes and at least one acaricide (IARC, 1978).

1.3. PRODUCTION DATA

According to the TSCA Production File (U.S. EPA, 1977), two U.S. companies, Pfister Chemical, Inc., Ridgefield, NJ, and DuPont Co., Deepwater, NJ, manufactured 4-chloro-2-methylaniline in 1977. Pfister Chemical, Inc. produced 10,000-100,000 pounds in 1977. As of January 1985, only Pfister Chemical Inc. was manufacturing this chemical in the United States (SRI, 1985); its recent production volume is not available. Three companies imported this chemical into the United States in 1977 (U.S. EPA, 1977). In 1983, 44,147 pounds of 4-chloro-2-methylaniline and its hydrochloride was imported in the United States (USITC, 1984). According to the TSCA Production File, the hydrochloride was not manufactured by any U.S. company in 1977, although Alliance Chemical Inc., Newark, NJ, did manufacture it before 1977 (U.S. EPA, 1977). Data in the available literature showed no indication that the hydrochloride is currently manufactured in the United States.

4-Chloro-2-methylaniline is prepared by the acetylation of toluidine with boiling acetic acid, chlorination of the acetyl-o-toluidine formed and saponification of the chlorinated product with sodium hydroxide (Hawley, 1981; Catino and Farris, 1978).

1.4. USE DATA

4-Chloro-2-methylaniline and its hydrochloride are used in the production of azo dyes. 4-Chloro-2-methylaniline, the free base, is also used as an intermediate in the production of pigments and in the production of chlordimeform, an insecticide and acaricide (IARC, 1978).

1.5. SUMMARY

Commercial 4-chloro-2-methylaniline is a crystalline, grayish white solid at ambient temperatures. It is sparingly soluble in water, but is soluble in ethanol and dilute acids (Hawley, 1981; Weast, 1980). The hydrochloride can be assumed to be soluble in water since the parent chemical is soluble in dilute acid (Hawley, 1981). As of January 1985, only Pfister Chemical Inc., Ridgefield, NJ, manufactured 4-chloro-2-methylaniline in the United States, but its recent production volume is not available (SRI, 1985). In 1983, 44,147 pounds of 4-chloro-2-methylaniline and its hydrochloride was imported in the United States (USITC, 1984). Data in the available literature showed no indication that the hydrochloride is currently manufactured in the United States (USITC, 1984). 4-Chloro-2-methylaniline is prepared by the acetylation of o-toluidine, chlorination of acetyl product and subsequent saponification of the chlorinated product. (Hawley, 1981; Catino and Farris, 1978). 4-Chloro-2-methylaniline and its hydrochlorible are used for the production of azo dyes. The free base, 4-chloro-2-methylaniline, is also used as an intermediate for the production of pigments and chlordimeform, an insecticide and acaricide (IARC, 1978).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Adequate data were not located in the available literature to assess the fate and transport of this chemical and its hydrochloride in the environment. Conclusions reached regarding the fate and transport of these chemicals are based on available experimental data and data for chemically similar compounds, and are speculative in nature. At typical environmental concentrations, it is anticipated that the hydrochloride will behave similarly to 4-chloro-2-methylaniline in the environment. Therefore, no additional data for the fate and transport of the hydrochloride have been evaluated.

2.1. WATER

Since 4-chloro-2-methylaniline has an absorption maximum at a wavelength of 296 nm (IARC, 1978), it will absorb radiation from natural sunlight and may undergo photoreactions. When 4-chloro-2-methylaniline was spotted on a silica gel plate and irradiated with sunlight in a greenhouse for 10 hours, $\geq$10 products were formed (Knowles and Gupta, 1969). Although none of these products were identified and the kinetics of this reaction was not studied, this experiment demonstrates the susceptibility of this compound to photoreaction in surface water by sunlight. Certain algae present in natural surface water can accelerate the photoreactions of aniline and substituted aniline (Zepp and Schlotzhauer, 1983). Algae had very little effect, however, on the photoreactivity of p-chloroaniline (Zepp and Schlotzhauer, 1983). Therefore, it is expected that algae also will not accelerate the photoreactivity of 4-chloro-2-methylaniline in surface waters.

The possibility of biodegradation of 4-chloro-2-methylaniline by both pure culture and mixed microorganisms was studied by a few investigators.

Bordeleau and Bartha (1972) isolated G. candidum L-3 from soil in which 4-chloro-2-methylaniline was biotransformed to its azo product. With well-acclimated activated sludge from an industrial wastewater treatment plant as microbial inoculum, Matsui et al. (1975) reported 7% total organic carbon removal in 24 hours for 4-chloro-2-methylaniline present at an initial concentration of 67 mg/ℓ. The removal of the parent compound during the same period was 33%. This indicates that although ~7% of the compound was completely mineralized, ~26% of it was metabolized into nonvolatilized products. These results and the results of soil biotransformation studies (Section 2.3.) indicate that 4-chloro-2-methylaniline will undergo biotransformation in water, although the quantitative significance of this process cannot be evaluated.

The loss of this compound in surface water through sorption onto suspended particulate matters and subsequent sedimentation, and evaporation to the atmosphere has not been studied. The possibility of strong sorption of unsubstituted and substituted aromatic amines onto the humic substances present in suspended particulates or sediments in surface water was demonstrated by Parris (1980). The covalent bonds formed between aromatic amines and the carbonyl group of humic substances will render this sorption process virtually irreversible. Thus, the portion of aquatic 4-chloro-2-methylaniline sorbed through such covalent binding may not be available for biotransformation, volatilization or other fate and transport processes. The soil study by Bollag et al. (1978) (Section 2.3.) indicates that this irreversible sorption process may be significant in water as well. The volatility study of 4-chloro-2-methylaniline in soil conducted by Bollag et al. (1978) can be used to predict the volatility of this compound from surface water. In a natural soil, ~2% of the compound volatilized in 40

days. When the soil was autoclaved, presumably eliminating the soil binding, ~12% of the compound volatilized during the same period. In surface water where the percentage of the covalent binding of the chemical to particulate matters is expected to be less than in natural soils, the volatilization is anticipated to be more rapid than in soil.

2.2. AIR

Information regarding the fate and transport of this compound in air could not be located in the available literature as cited in the Appendix. Based on the photolysis experiments of the compound coated on silica gel (see Section 2.1.) (Knowles and Gupta, 1969), it is speculated that direct photolysis of this compound will occur in the atmosphere. The reactivity of 4-chloro-2-methylaniline toward OH radical is expected to be similar to that of p-chloroaniline. By using the rate constant for p-chloroaniline reaction with OH radical in the atmosphere of 83×10^{-12} cm^3 $molecule^{-1}$ sec^{-3} (Atkinson, 1985) and assuming the concentration of OH radical in ambient air to be 10^6 molecules cm^{-3} (U.S. EPA, 1980), the half-life for this reaction is estimated as 2.3 hours. Therefore, because of the expected similarity in reactivity, this reaction may also be the fate-determining process for 4-chloro-2-methylaniline in the atmosphere.

2.3. SOIL

From the photolysis experiment by Knowles and Gupta (1969) with 4-chloro-2-methylaniline coated on silica gel plates, it can be concluded that photolysis may be significant on soil surfaces; however, light scattering and attenuation will render the photolysis process ineffective in the interior soil layers. Bordeleau and Bartha (1972) studied the biodegradation of this compound with Nixon sandy loam soil, and found evidence of transformation of 4-chloro-2-methylaniline into a diazotized product. When

4-chloro-2-methylaniline was incubated with a natural soil, Bollag et al. (1978) reported 20% mineralization of the compound in 6 weeks, compared with 0% mineralization in sterilized soil.

Bollag et al. (1978) reported that only 2% of the compound volatilized in 40 days from an unsterilized soil with 3.4% organic matter content. When the soil was sterilized, however, the volatility increased to 12% in 40 days; this was presumably due to the weakening of the covalent bonds between the chemical and the carbonyl groups of humic materials in soil. The possibility of irreversible covalent binding between aromatic amines and carbonyl groups in humic materials was studied by Parris (1980). Although 4-chloro-2-methylaniline was not specifically studied, other similar substituted amines, including 4-methylaniline and 4-chloroaniline, reportedly formed irreversible covalent bonds with humic substances. Evidence of this irreversible sorption in the case of 4-chloro-2-methylaniline was provided by the experiment of Bollag et al. (1978). When the compound was incubated with a nonautoclaved soil (3.4% organic matter content), only 6.2% of the compound present in the soil after 42 days was recoverable by methanol Soxhlet extraction; 61.7% of the residue still remained in the soil. These experiments indicate that 4-chloro-2-methylaniline will be sorbed strongly onto soil and therefore, significant leaching of this material from soil is unlikely. In sandy soil where the sorption of the compound will be low and in soil where the microbial population is small because of the toxicity associated with the soil (e.g., waste disposal site, spillage), leaching of the chemical may occur.

2.4. SUMMARY

Adequate data are not available in the literature to assess the environmental fate and transport of 4-chloro-2-methylaniline or its hydrochloride.

The conclusions reached regarding the fate and transport of 4-chloro-2-methylaniline and its hydrochloride in different media are based on experimental data for this chemical and data for chemically similar compounds. Based on the photolysis experiment of Knowles and Gupta (1969), it has been concluded that direct photolysis may be a significant fate process for this chemical in water, although no half-life from this reaction can be derived. The biodegradation study results of Matsui et al. (1975) indicate that 4-chloro-2-methylaniline will undergo biotransformation in water, but the quantitative significance of this process in determining the overall fate of 4-chloro-2-methylaniline in water cannot be evaluated. Based on the soil study by Bollag et al. (1978), it has been concluded that sorption may be a significant process in water. The volatilization of this chemical from water may not be significant in water containing humic materials in suspended particulates.

In air, the reaction of this chemical with OH radical may be the fate determining process. Based on the rate constant for OH radical reaction with a similar compound (Atkinson, 1985), the estimated half-life of this reaction is ~3 hours.

Biodegradation may be an important fate-determining process for this chemical in soil. Bollag et al. (1978) reported 20% mineralization of the compound in 6 weeks when incubated with a natural soil. Only 2% of the compound volatilized in 40 days from a soil containing 3.4% organic matter. The binding of the chemical in soil was strong; of the total amount of the compound applied to a soil containing 3.4% organic matter, ~61.7% of the residue remained irreversibly sorbed to soil after 42 days. Therefore, significant leaching of this material from most soils is unlikely, although leaching may occur in sandy soils and in soils from waste disposal and spillage sites.

3. EXPOSURE

4-Chloro-2-methylaniline and its hydrochloride do not occur as natural products. 4-Chloro-2-methylaniline can be formed from the metabolism of chlordimeform when applied as an insecticide and acaricide on apples and cotton plants (IARC, 1978). Consumer exposure to these compounds through residues present in azo dyes used for dyeing cotton, silk, acetate and rayon, is also possible. These compounds are also likely to be present in wastewaters from the azo dye industry; however, apparently neither of these compounds have ever been reported in water, air or foods. The absence of data on the level of these compounds in the environment in the United States may be due partly to lack of appropriate monitoring and partly because these compounds are manufactured in a limited number of sites.

3.1. SUMMARY

Neither 4-chloro-2-methylaniline nor its hydrochloride has apparently ever been detected in water, air or foods.

4. PHARMACOKINETICS

4.1. ABSORPTION

Knowles and Gupta (1970) reported that 71% of the radioactivity of an unspecified oral dose of 4-chloro-2-[methyl-^{14}C]aniline was eliminated within 72 hours in the urine of Sprague-Dawley rats. Fecal excretion accounted for 24.5%. These data suggest that 4-chloro-2-methylaniline is substantially (at least 71%) absorbed by the gastrointestinal tract. Data regarding the absorption of 4-chloro-2-methylaniline hydrochloride are limited; however, absorption of the hydrochloride from the gastrointestinal tract can be inferred from the systemic toxicity and the development of tumors following chronic administration in the diet (Section 5.1.).

4.2. DISTRIBUTION

4-Chloro-2-methylaniline and its hydrochloride appear to be widely distributed to the tissues of rats. Seventy-two hours following oral administration of an unspecified dose of 4-chloro-2-[methyl^{14}C]aniline to two male and two female Sprague-Dawley rats, the highest levels of radioactivity were found in the fat, liver and kidney (Knowles and Gupta, 1970). Radioactivity was also found in the oviducts, brain, heart, lung, muscle, plasma, spleen, testes and intestines.

Hill et al. (1979) studied <u>in vivo</u> binding of radioactivity to protein, DNA and RNA in various tissues of five adult Osborne-Mendel rats 24 hours after intraperitoneal injection with 14 mg/kg of 4-chloro-2-[methyl^{14}C]-aniline hydrochloride. The largest amount of radioactivity was bound to macromolecules of the liver. The brain, heart, testis, muscle, lung and spleen contained the least binding, while the kidney, stomach, large and small intestine were intermediate in irreversible binding of radioactivity.

4.3. METABOLISM

Knowles and Gupta (1970) reported that an unspecified oral dose of 4-chloro-2-[methyl-^{14}C]aniline was extensively metabolized; by 72 hours after treatment, only 3.7% of the recovered radioactivity (<1% of applied radioactive dose) in the urine was the parent compound. Of the radioactive materials in the urine 50% were ethyl acetate extractable. In this fraction, 5-chloroanthranilic acid and 4-chloro-2-methylacetanilide were identified as metabolites by TLC. Other extractable radioactive materials and unextractable substances in the urine were not identified. The highest percentage of 5-chloroanthranilic acid was extracted from urine after 3 hours, while the concentration of 4-chloro-2-methylacetanilide was greatest 48 hours after administration. The authors postulated that 5-chloroanthranilic acid was formed by oxidation of the methyl group. 4-Chloro-2-methylacetanilide appears to have been formed by acetylation of the amine group.

In vitro metabolism and macromolecular binding of 4-chloro-2-[methyl-^{14}C]aniline hydrochloride was studied in liver microsomes from phenobarbital-induced Osborne-Mendel rats (Hill et al., 1979). Radioactivity was irreversibly bound to microsomal macromolecules. The nature of the bound radioactivity, however, was not identified. 4-Chloro-2-methylaniline hydrochloride was a substrate for rat liver microsomes. The reaction was dependent on NADPH and increased with phenobarbital pretreatment, indicating cytochrome P450 involvement in metabolism of the compound. 5-Chloro-2-hydroxylaminotoluene was identified as the major metabolite, formed by microsomal oxidation of the parent compound. The authors postulated that further oxidation of the major metabolite to a nitroso intermediate occurred, leading to the formation of the minor metabolite, 4,4'-dichloro-2,2'-dimethylazobenzene.

The possible routes of metabolism of 4-chloro-2-methylaniline and its hydrochloride compiled from the previously-mentioned *in vivo* and *in vitro* studies are shown in Figure 4-1.

4.4. EXCRETION

Knowles and Gupta (1970) reported that 71 and 24.5% of the radioactivity of an unspecified oral dose of 4-chloro-2-[methyl-^{14}C]aniline was eliminated in 72 hours in the urine and feces, respectively, of Sprague-Dawley rats. Identification of urine constituents by TLC demonstrated that both parent compound and metabolites were eliminated in the urine. The maximum concentration of the radioactivity in both urine and feces was found 12 hours after oral administration.

4.5. SUMMARY

4-Chloro-2-methylaniline and its hydrochloride appear to be substantially absorbed from the gastrointestinal tract and widely distributed to tissues of rats. The distribution of the two compounds appears to be similar. Knowles and Gupta (1970) reported that the highest levels of radioactivity 72 hours after an unspecified oral dose of 4-chloro-2-[methyl^{14}C]aniline to male and female Sprague Dawley rats were found in the fat, liver and kidneys. Hill et al. (1979) reported that irreversible binding of radioactivity to macromolecules was greatest in the liver of Osborne-Mendel rats treated intraperitoneally with 4-chloro-2-[methyl-^{14}C]aniline hydrochloride.

The metabolism of 4-chloro-2-methylaniline and its hydrochloride has been studied *in vivo* and *in vitro*, respectively. These studies suggest that 4-chloro-2-methylaniline and its hydrochloride are metabolized by hepatic P-450 enzymes. Based on metabolites identified in various studies, it has

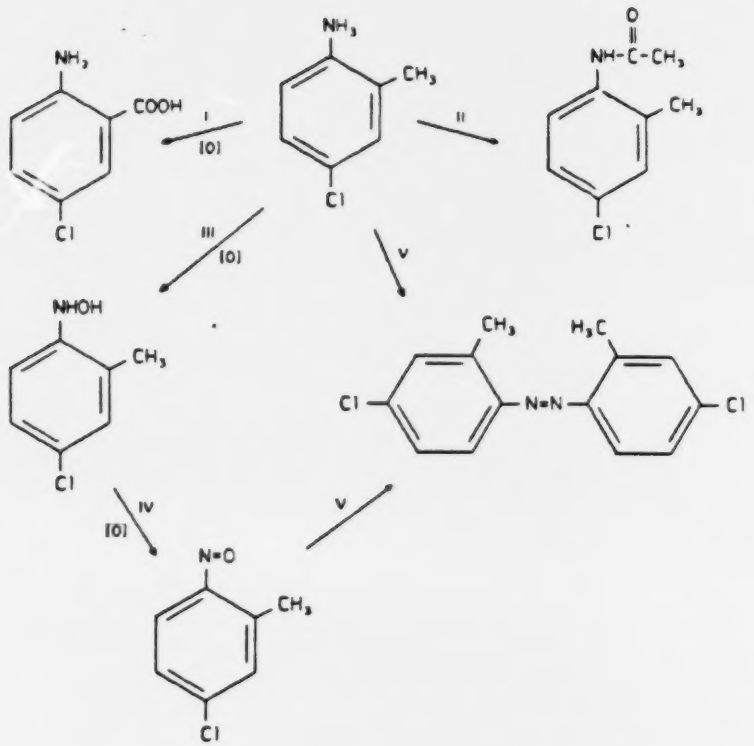


FIGURE 4-1

Possible Routes of Metabolism of 4-Chloro-2-methylaniline and Its Hydrochloride

I. Oxidation of methyl group (Knowles and Gupta, 1970)
II. Acetylation of amino group (Knowles and Gupta, 1970)
III. Oxidation of amino group (Hill et al., 1979), in vitro using the hydrochloride)
IV. Oxidation of hydroxylamino group [intermediate proposed by Hill et al. (1979)]
V. Condensation (Hill et al., 1979)

been suggested that 4-chloro-2-methylaniline is oxidized to 5-chloroanthranilic acid and 5-chloro-2-hydroxylaminotoluene, acetylated to 4-chloro-2-methylacetanilide and condensed to form 4,4'-dichloro-2,2'-dimethylazobenzene (Knowles and Gupta, 1970; Hill et al., 1979).

Knowles and Gupta (1970) reported that 4-chloro-2-methylaniline and its metabolites were excreted in the urine and feces. Of the radioactivity of an unspecified oral dose of the radiolabeled parent compound, 71% was eliminated in the urine and 24.5% was eliminated in feces within 72 hours of administration.

5. EFFECTS

5.1. CARCINOGENICITY

Only 4-chloro-2-methylaniline hydrochloride has been tested for potential carcinogenicity. In an NCI (1978) bioassay, 50 male and 50 female Fischer 344 rats were fed 1250 or 5000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet for 107 weeks, and then sacrificed. Twenty untreated rats of each sex were used as the matched controls. There was no statistically significant dose-related trend in mortality in either sex. At the end of the bioassay, 41/50 males and 45/50 females of the high-dose group, 38/50 males and 42/50 females of the low-dose group, and 11/20 males and 15/20 females of the controls survived. Sufficient numbers of rats were at risk for development of late-appearing tumors. All rats that died or were killed in a moribund condition or that were killed at the end of the study were necropsied and given comprehensive gross and histological examinations, unless precluded by autolysis or cannibalism. Table 5-1 shows the incidence of pituitary chromophobe adenomas in male and female rats. The incidences in low- and high-dose females were significantly greater than control (Fisher Exact test) but the p value for a dose-related trend was not significant. A significant dose-related trend (Cochran-Armitage test) in the incidence of pituitary chromophobe adenomas in male rats was observed, but the incidences were not significantly greater than control. Although the increased incidence of the benign pituitary tumors in both sexes appears to be treatment-related, this tumor type was found in historical controls at higher incidences (18% in male and 21% in female historical controls) and was not considered to be attributable to dietary administration of 4-chloro-2-methylaniline hydrochloride.

TABLE 5-1

Incidence of Tumors in Rats and Mice Treated with 4-Chloro-2-methylaniline Hydrochloride (>99% pure) in the Diet[a,b]

Species/Strain	Sex	Dose (ppm)	Duration of Treatment (weeks)	Target Organ	Tumor Type	Tumor Incidence[c] (p value)[d]
Rat/F344	F	0	NA	pituitary	adenoma	1/19 (NS)
		1250	107	pituitary	adenoma	13/47 (p=0.039)
		5000	107	pituitary	adenoma	15/48 (p=0.020)
	M	0	NA	pituitary	adenoma	2/19 (p=0.006)
		1250	107	pituitary	adenoma	6/48 (NS)
		500	107	pituitary	adenoma	15/47 (NS)
Mouse/B6C3F1	M	0	NA	all sites	hemangiosarcoma	0/20 (p<0.001)
				all sites	hemangiosarcoma/hemangioma	0/20 (p<0.001)
		3750	99	all sites	hemangiosarcoma	3/50 (NS)
				all sites	hemangiosarcoma/hemangioma	6/50 (NS)
		15,000	99	all sites	hemangiosarcoma	37/50 (p<0.001)
				all sites	hemangiosarcoma/hemangioma	41/50 (p<0.001)
	F	0	NA	all sites	hemangiosarcoma	0/18 (p<0.001)
				all sites	hemangiosarcoma/hemangioma	1/18 (p<0.005)
		1250	99	all sites	hemangiosarcoma	40/49 (p<0.001)
					hemangiosarcoma/hemangioma	44/49 (p<0.001)
		5000	92	all sites	hemangiosarcoma	39/50 (p<0.001)
				all sites	hemangiosarcoma/hemangioma	39/50 (p<0.001)

QUALITY OF EVIDENCE

Strengths of Study: Compound was administered by a relevant route of exposure at two doses in both sexes of two species. Adequate numbers of animals survived to be at risk for late-appearing tumors.

Overall Adequacy: Adequate

[a]Source: NCI, 1978

[b]The duration of the study was equal to the duration of the treatment.

[c]Tumor incidence expressed as number of animals with tumors/number of animals examined microscopically.

[d]The p value for the Cochran-Armitage test for linear trend is shown next to the control incidence; the p value for the Fisher Exact test is shown next to the incidence in the treated group.

NA = Not applicable; NS = not stated

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In the same study (NCI, 1978), groups of 50 male B6C3F1 mice were fed 3750 or 15,000 ppm and 50 female mice were fed 1250 ppm of 4-chloro-2-methylaniline hydrochloride in the diet for 99 weeks and then sacrificed. Another group of 50 female mice was administered 5000 ppm, but this treatment was terminated at 92 weeks because all the mice died. Matched control groups consisted of 20 untreated mice of each sex. There was a significant dose-related trend (Tarone test) for increased mortality for each sex. At 52 weeks, all males had survived, but at 90 weeks, survival had decreased in the high-dose males to ~55%. Survival of the low-dose males was comparable to controls. In the females, >95% of the mice in each group survived until week 60, but by 75 weeks of treatment survival had decreased to ~35% in the high-dose and 85% in the low-dose groups. All mice that died or were killed in a moribund condition, or that were killed at the end of the study were necropsied and given comprehensive gross and histological examinations, unless precluded by autolysis or cannibalism. As shown in Table 5-1, there was a significant dose-related increase in hemangiosarcomas in both sexes. These tumors appeared to originate in fatty tissue adjacent to the genital organs and were lethal to 75% of the affected mice because of hemorrhaging in the peritoneal cavity. The increased incidence of hemangiosarcomas in male mice in the high-dose group, compared with controls, was statistically significant alone and when combined with incidence data for hemangiomas. The incidences in the low-dose males were not significantly higher than control. In the female mice, both treated groups showed a statistically significant (Fisher Exact Test) increase in hemangiosarcomas and in hemangiosarcomas and hemangiomas combined.

Weisburger et al. (1978) administered 4-chloro-2-methylaniline hydrochloride in the diet to male Charles River CD rats and Charles River CD-1 mice of both sexes for 18 months and then sacrificed the rats 6 months later and the mice 3 months later. Groups of 25 rats received 2000 or 4000 ppm for 3 months; however, because of mortality or a decrease in body weight >10% (relative to controls), dose levels were reduced to 500 or 1000 ppm for the remaining 15 months, producing TWA doses of 750 and 1500 ppm. Groups of 25 male mice were fed 750 or 1500 ppm, while groups of 25 females were fed 2000 or 4000 ppm of 4-chloro-2-methylaniline hydrochloride. Simultaneous control groups consisted of 25 male rats and 25 mice of each sex, and pooled controls consisted of 125 male rats and 125 mice of each sex. A histological examination was performed on all grossly abnormal organs, tumor masses, lung, liver, spleen, kidney, adrenal, heart, bladder, stomach, intestines, reproductive organs and rat pituitary in animals that died after 6 months or were sacrificed at termination of the study. Tumor incidences were statistically analyzed by the Fisher Exact test relative to simultaneous and pooled controls. No statistically significant increased incidence of tumors was found in treated rats relative to controls. In both sexes of mice and at both doses, there was a significant increase in the incidence of vascular hemangiosarcomas/hemangiomas, particularly in the spleen and subcutaneous or subperitoneal fat. Multiple tumors (type or target organs were not specified) were significantly increased in low-dose male mice when compared with pooled controls, but not when compared with matched controls (Table 5-2).

5.2. MUTAGENICITY

4-Chloro-2-methylaniline did not induce reverse mutations in Salmonella typhimurium strains TA98, TA100, TA1537, TA1538 at concentrations of 1-325 µg/plate, with or without S-9 activation (Rashid et al., 1984). E. coli

TABLE 5-2

Tumor Incidence in CD-1 Mice Administered 4-Chloro-2-methylaniline Hydrochloride (>97%) in the Diet for 18 Months and Examined After 21 Months[a]

Sex	Dose (mg/kg)	Target Organ	Tumor Type	Tumor Incidence[b] (p value)
M	0[c]	vascular	hemangiosarcoma/hemangioma	0/14
		NR	multiple tumors	1/14
	0[d]	vascular	hemangiosarcoma/hemangioma	5/99
		NR	multiple tumors	14/99
	750	vascular	hemangiosarcoma/hemangioma	12/20[e]
		NR	multiple tumors	7/20[f]
	1500	vascular	hemangiosarcoma/hemangioma	13/20[e]
		NR	multiple tumors	6/20
F	0[c]	vascular	hemangiosarcoma/hemangioma	0/15
	0[d]	vascular	hemangiosarcoma/hemangioma	9/102
	2000	vascular	hemangiosarcoma/hemangioma	18/19[e]
	4000	vascular	hemangiosarcoma/hemangioma	12/16[e]

QUALITY OF EVIDENCE

Strengths of Study: Two species were administered the compound by a relevant route of exposure at two doses. Adequate numbers of animals survived to be at risk for late developing tumors.

Weakness of Study: Only male rats were tested and the duration of treatment was relatively short for carcinogenicicty studies.

Overall Adequacy: Adequate

[a] Source: Weisburger et al., 1978

[b] Method for reporting tumor incidence was not specified

[c] Simultaneous controls

[d] Pooled controls

[e] Significant difference from incidence in all controls, comparing treated with controls ($p<0.025$)

[f] Significant difference from incidence in all pooled controls only ($0.025<p<0.05$)

NR = Not reported

strains WP_2, WP_2uvrA, WP67, CM611, CM571 when exposed to discs impregnated with 250-2000 mg/disc of 4-chloro-2-methylaniline also did not show increased revertants with or without S-9 (Rashid et al., 1984). Only S. typhimurium strain TA1535, when tested without metabolic activation at higher concentrations (100-600 µg/plate), showed a positive mutagenic response.

4-Chloro-2-methylaniline hydrochloride also produced negative results for mutagenicity in S. typhimurium strains TA98, TA1535 and TA1357 when tested both with or without S-9 activation (Zimmer et al., 1980; Haworth et al., 1983). Equivocal results for the induction of reverse mutations by 4-chloro-2-methylaniline hydrochloride in S. typhimurium strain TA100 have been reported. Zimmer et al. (1980) found positive results using S-9 activation, whereas Haworth et al. (1983) found negative results both with and without metabolic activation.

Inhibition of growth was measured as an indication of DNA damage using the Salmonella DNA repair system TA1538/TA1978 and E. coli DNA repair-proficient and deficient (WP_2uvrA; CM611) strains (Rashid et al., 1984). High concentrations of 4-chloro-2-methylaniline (250-2000 mg/disc) inhibited growth of the DNA repair-deficient strains of both organisms to a greater extent than the repair-proficient strains. Zimmer et al. (1980) analyzed DNA damage in Chinese hamster lung fibroblasts (V79 cells) by alkaline elution. 4-Chloro-2-methylaniline induced DNA damage in these cells with S-9 activation, following 2 and 4 hours of in vitro exposure at concentrations $\geq$3 mM. In another in vitro assay, 4-chloro-2-methylaniline inhibited cell growth and RNA synthesis by 38% at 10^{-3} M in cultured HeLa cells (Murakami and Fukami, 1974). The ID_{50} was 10^{-4} M.

Two *in vivo* mutagenicity assays have reported positive results for 4-chloro-2-methylaniline (Seiler, 1977; Lang, 1984), while negative results have been reported for the hydrochloride (Lang and Adler, 1982). Coat color spots, which are indicative of mutations at recessive gene coat color loci in C57B1/6J mice, were observed in the progeny of dams given 100 mg/kg of 4-chloro-2-methylaniline hydrochloride in water by gavage on days 8, 9 and 10 of pregnancy (Lang, 1984). Seiler (1977) reported inhibition of testicular DNA synthesis, as quantitated by [^{3}H]-thymidine incorporation, in male mice orally administered 200 mg/kg of 4-chloro-2-methylaniline. Male progeny of male NMRI/SPF mice treated by gavage with 200 mg/kg/day of 4-chloro-2-methylaniline hydrochloride in water for an entire spermatogenic cycle (7 weeks) showed no reduced fertility (Lang and Adler, 1982). Sterility or a decrease in fertility would have been evidence for animals carrying reciprocal translocations.

The mutagenicity studies are summarized in Table 5-3.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of 4-chloro-2-methylaniline or its hydrochloride salt could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Lang and Adler (1982) treated male NMRI/SPF mice by gavage for 7 weeks (length of the spermatogenic cycle) with 200 mg/kg/day of 4-chloro-2-methylaniline hydrochloride in water. Fertility (i.e., percent fertile matings and mean viable litter size) following treatment was not altered.

Female C57BL/6J mice treated by gavage on days 8, 9 and 10 of pregnancy with 100 mg/kg 4-chloro-2-methylaniline hydrochloride in water showed no difference in numbers of litters or number of offspring surviving until 4 weeks of age relative to vehicle controls (Lang, 1984).

TABLE 5-3

Mutagenicity Testing of 4-Chloro-2-methylaniline and its Hydrochloride

Assay	Indicator/ Organism	Compound* and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA100 TA98 TA1537	hydro-chloride/ >97%	plate incorporation	0.025-1.4 µmol/plate	+S-9	+ - -	NC	Zimmer et al., 1980
Reverse mutation	S. typhimurium TA100 TA1535 TA1537 TA98	hydro-chloride/ >99%	plate incorporation	1-3333 µg/plate	±S-9	= = = =	Strains were pre-incubated with compound before plating	Haworth et al., 1983
Reverse mutation	S. typhimurium TA1535	99%	plate incorporation	100-600 µg/plate	-S-9	+	NC	Rashid et al., 1984
Reverse mutation	S. typhimurium TA1537 TA1538 TA98 TA100	99%	plate incorporation	1-325 µg/plate	±S-9	= = = =	NC	Rashid et al., 1984
Reverse mutation	E. coli WP_2 WP_2uvr WP67 CM611 CM571	99%	disc	250-2000 mg/disc	±S-9	= = = = =	NC	Rashid et al., 1984
DNA repair	S. typhimurium TA1538/1978	99%	disc	250-2000 mg/disc	-S-9	+	Positive result indicates greater zone of inhibition in deficient strain than in proficient strain	Rashid et al., 1984
DNA repair	E. coli WP_2 WP_2uvrA WP67 CM611 CM571	99%	disc	250-2000 mg/disc	-S-9	+ + + + +	Positive result indicates greater zone of inhibition in repair-deficient than in repair-proficient strain	Rashid et al., 1984

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TABLE 5-3 (cont.)

Assay	Indicator/ Organism	Compound* and/or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
DNA breakage	Chinese hamster lung fibroblasts (V79 cells)	>97%	NR	0.3-10 mM 2-4 hours	+S-9	+	+ at ≥3 mM; DNA damage measured by alkaline elution; toxicity after 4 hours at 10 mM/l.	Zimmer et al., 1980
Cell growth and RNA synthesis	HeLa cells	NR	plate incorporation	10^{-4} M	none	+	Inhibition of cell growth $ID_{50}=10^{-4}$ M (by interpolation); 38% inhibition of RNA synthesis	Murakami and Fukami, 1974
Inhibition of testicular DNA synthesis	mice	NR	oral	200 mg/kg	none	+	26% [^{3}H]-thymidine incorporation of concurrent controls	Seiler, 1977
Heritable translocation	mice NMRI/SPF	hydrochloride/ NR	oral	200 mg/kg/day for 7 weeks	none	-	NC	Lange and Adler, 1982
Mammalian spot test	mice C57BL/6J	hydrochloride/ NR	oral to dam	100 mg/kg on days 8, 9, 10 of gestation	none	+	NC	Lang, 1984

*4-Chloro-2-methylaniline, unless specified as hydrochloride

NR = Not reported; NC = no comment

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Pertinent data regarding the chronic and subchronic toxicity of 4-chloro-2-methylaniline could not be located in the available literature, but information regarding the chronic and subchronic toxicity of its hydrochloride was found in an NCI (1978) carcinogenicity bioassay.

In preliminary subchronic studies conducted to determine the MTD for the chronic bioassay (NCI, 1978), groups of five Fisher 344 rats and five B6C3F1 mice of each sex were maintained at various concentrations of 4-chloro-2-methylaniline hydrochloride in the diet for 7 weeks. Controls were fed basal diet. Male rats were treated at 250-10,000 ppm of the compound in the diet. There was no effect on survival, but slightly decreased body weight (1-11%) was reported at week 7 at all doses. The decreases were not dose-related. Female rats were fed dietary concentrations of 1000-50,000 ppm of 4-chloro-2-methylaniline hydrochloride. Body weight at 7 weeks did not appear to be altered at doses <4000 ppm, but a dose-related decrease in weight occurred at doses >6200 ppm. No mortality occurred in the females at doses <25,000 ppm, but 100% mortality occurred at 50,000 ppm. Slight splenomegaly was noted in male rats at 6500 ppm and was observed in both sexes at 10,000 ppm.

Male mice had slightly decreased body weight at 4000-10,000 and 11% decrease at 15,000 ppm. No deaths occurred following administration of 4000-15,000 ppm of 4-chloro-2-methylaniline in the diet for 7 weeks. In female mice, body weight decreased by 10-22% at concentrations of 15,000-20,000 ppm, but no mortality occurred.

In the chronic bioassay (NCI, 1978) (see Section 5.1.), mean body weights of high-dose (5000 ppm) male and female rats were slightly less than controls following 30 weeks of treatment. Statistical analyses (Tarone

test) showed no significant dose-related trend in mortality in either sex of rats, with >75% of the treated rats surviving until the end of the bioassay. No treatment-related increased incidences of nonneoplastic lesions were observed.

Mean body weights of mice showed dose-related decreases of ~10-20% for the males and 20-50% for the females throughout the duration of the bioassay (NCI, 1978). Survival of both sexes was decreased in the high-dose groups after ~60 weeks of administration of 4-chloro-2-methylaniline hydrochloride in the diet. Low-dose female mice also had decreased survival relative to controls after ~70 weeks of treatment. The mortality appeared to be secondary to tumor development since 89/119 hemangiosarcoma-bearing treated mice (see Section 5.1.) died from hemorrhage and invasion of tumors into the peritoneal cavity. Spleen enlargement was observed in treated mice and was due to extramedullary hematopoiesis in response to the hemorrhage. A high incidence of hemosiderin deposits in the renal tubule epithelium occurred in mice with hemangiosarcomas. Hemosiderosis occurred in females at incidences of 0/18 in controls, 18/49 in the low-dose group and 16/48 in the high-dose group, and in males at 0/20 in controls, 1/50 in the low-dose group and 7/50 in the high-dose group. Thus, it appears that the nonneoplastic effects were secondary to the development of hemangiosarcomas. Kidney hemosiderosis was found in treated male mice.

In the carcinogenicity study by Weisburger et al. (1978) (see Section 5.1.), dosage levels of 4-chloro-2-methylaniline hydrochloride in the diet fed to rats were reduced from 2000 and 4000 mg/kg to 500 and 1000 mg/kg, respectively, after 12 weeks; this was attributed to either mortality or a decrease in body weight of >10% relative to controls. Data for body weight or mortality were not provided.

5.6. OTHER RELEVANT INFORMATION

Currie (1933) reported 11 cases of poisoning by 4-chloro-2-methylaniline or its hydrochloride (or both) in workers involved with the manufacture of these compounds. Within days of the first exposure, the workers developed symptoms of suprapubic pain, frequent urination, hematuria and exfoliation of the bladder epithelium.

The intraperitoneal LD_{50} for 4-chloro-2-methylaniline hydrochloride in mice was reported to be 720 and 680 mg/kg for males and females, respectively, and for rats was 560 and 700 mg/kg for males and females, respectively (Weisburger et al., 1978).

Schafer and Bowles. (1985) estimated an oral LD_{50} of >375 mg/kg for deer mice, Peromyscus maniculatus, based on consumption of Douglas fir seeds treated with 4-chloro-2-methylaniline for 3 days.

Kimbrough (1980) treated two cats with 50 mg of 4-chloro-2-methylaniline subcutaneously. It was not clear if the cats received a single dose or 5 daily doses of 50 mg/cat. At sacrifice 4 days later after the last dose, the bladder mucosa appeared edematous and congested and hepatocytes were vacuolated.

4-Chloro-2-methylaniline was a weak inhibitor of rat brain monoamine oxidase ($IC_{50}=1.10^{-4}$ M) when measured in vitro in whole brain homogenates (Benezet and Knowles, 1976).

5.7. SUMMARY

Only 4-chloro-2-methylaniline hydrochloride has been tested for carcinogenicity. In an NCI (1978) bioassay, no increased incidences of tumors occurred in male or female Fischer 344 rats fed 1250 or 5000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet for 107 weeks. The incidence of hemangiosarcomas was significantly increased in males treated at 3750 and 15,000 ppm and in female mice treated at 1250 or 5000 ppm for

92-99 weeks relative to controls. In another study, no increase in tumor incidence was reported in male rats treated at dietary levels of 750 or 1500 ppm compared with controls (Weisburger et al., 1978). Male mice treated at 750 or 1500 ppm and female mice treated at 2000 or 4000 ppm, however, had a significant dose-related increase in incidence of vascular hemangiosarcomas and hemangiomas relative to controls.

4-Chloro-2-methylaniline did not induce reverse mutations in most strains of S. typhimurium or in E. coli with or without S-9 activation (Rashid et al., 1984); however, the compound inhibited growth of DNA repair-deficient strains of S. typhimurium and E. coli (Rashid et al., 1984). 4-Chloro-2-methylaniline induced DNA damage in Chinese hamster lung fibroblasts (Zimmer et al., 1980) and inhibited cell growth and RNA synthesis in HeLa cells (Murakami and Fukami, 1974). Positive results have also been reported for inhibition of testicular DNA synthesis in male mice (Seiler, 1977) and for mutations at recessive gene coat color loci in mice (Lang, 1984).

4-Chloro-2-methylaniline hydrochloride produced negative results for mutations in most S. typhimurium strains, with or without S-9 addition (Zimmer et al., 1980; Haworth et al., 1983), but equivocal results were found in strain TA100. Negative results were reported in the heritable translocation assay (Lang and Adler, 1982).

Fertility of male NMRI/SPF mice was not affected following oral treatment with 200 mg/kg/day 4-chloro-2-methylaniline hydrochloride (Lang and Adler, 1982). No differences in number or viability were found in litters of female C57BL/6J mice treated by gavage with 100 mg/kg of the compound on days 8, 9 and 10 of pregnancy (Lang, 1984). Pertinent data regarding the teratogenicity of 4-chloro-2-methylaniline or its hydrochloride salt were not available.

Subchronic studies of 4-chloro-2-methylaniline hydrochloride showed no effect on survival but a slight but not dose-related decrease in body weight in male Fischer rats fed 250-10,000 ppm in the diet for 7 weeks (NCI, 1978). Splenomegaly was noted in males at doses ≥6500 ppm. At doses ≥6200 ppm, a dose-related decrease in body weight occurred in female rats administered the compound in the diet for 7 weeks. Mortality was 100% in the female rats occurred at 50,000 ppm. Male mice showed a slight but not dose-related decrease in body weight, but no mortality after 7 weeks of treatment with 2000-15,000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet (NCI, 1978). At concentrations of 15,000-20,000 ppm, no mortality occurred in female mice, but body weight was decreased by 10-20% after 7 weeks.

Chronic toxicity data from the NCI (1978) bioassay showed a slight decrease in body weight of high-dose (5000 ppm) male and female rats relative to controls after 30 weeks of treatment with 4-chloro-2-methylaniline hydrochloride in the diet. Survival of both dose groups of female mice (1250 and 5000 ppm) and high-dose male mice (15,000 ppm) was decreased after 60 weeks of treatment. The high mortality was secondary to tumor development. Mean body weights of both sexes of mice showed a dose-related decrease throughout the bioassay. Kidney hemosiderosis was apparent in both sexes of mice but was related to tumor development.

Irritation of the bladder has been reported in 11 workers involved in the manufacture of 4-chloro-2-methylaniline (Currie, 1933) and in cats treated subcutaneously with the compound (Kimbrough, 1980). The intraperitoneal LD_{50} for mice was 680-720 mg/kg and 560-700 mg/kg for rats (Weisburger et al., 1978). 4-Chloro-2-methylaniline inhibited rat brain monoamine oxidase *in vitro* (Benezet and Knowles, 1976).

6. AQUATIC TOXICITY

6.1. ACUTE

Pertinent data regarding the acute toxicity of 4-chloro-2-methylaniline or its hydrochloride to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of 4-chloro-2-methylaniline or its hydrochloride to aquatic organisms could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding effects of 4-chloro-2-methylaniline or its hydrochloride on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

In the algae, Chorella sp. and Oscillatoria sp. incubated with radiolabeled chlordimeform for 14 days, residues of 4-chloro-2-methylaniline accounted for 31 and 19% of the total radioactivity isolated (Benezet and Knowles, 1981). In another experiment in which algae were exposed to radiolabeled 4-chloro-o-formotoluidine for 14 days, 4-chloro-2-methylaniline accounted for 34 and 17% of the radioactivity recovered from Chlorella sp. and Oscillatoria sp., respectively (Benezet and Knowles, 1981).

6.5. SUMMARY

There was no information available concerning the toxicity of 4-chloro-2-methylaniline or its hydrochloride to aquatic organisms. 4-Chloro-2-methylaniline was one of the principal metabolites formed by the algae Chlorella sp. and Oscillatoria sp. exposed to chlordimeform or 4-chloro-o-formotoluidide (Benezet and Knowles, 1981).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent guidelines and standards, including EPA ambient water and air quality criteria, drinking water standards, FAO/WHO ADIs, EPA or FDA tolerances for raw argicultural commodities or foods, and ACGIH, NIOSH or OSHA occupational exposure limits could not be located in the available literature as cited in the Appendix.

7.2. AQUATIC

Guidelines and standard for the protection of aquatic biota from the effects of 4-chloro-2-methylaniline and 4-chloro-2-methylaniline hydrochloride could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Only 4-chloro-2-methylaniline hydrochloride has been tested for carcinogenicity. In an NCI (1978) bioassay, no increased incidence of tumors occurred in male and female Fischer 344 rats fed 1250 or 5000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet for 107 weeks. The incidence of hemangiosarcomas was significantly increased in male mice treated at 3750 and 15,000 ppm and in female mice treated at 1250 or 5000 ppm for 92-99 weeks, relative to controls. In another study, no increase in tumor incidence was reported in male rats treated at dietary levels of 750 or 1500 ppm as compared with controls (Weisburger et al., 1978). Male mice treated at 750 and 1500 ppm and female mice treated at 2000 or 4000 ppm, however, had a significant dose-related increase in incidence of vascular hemangiosarcomas and hemangiomas relative to controls.

4-Chloro-2-methylaniline did not induce reverse mutations in most strains of S. typhimurium or in E. coli with or without S-9 activation (Rashid et al., 1984); however, the compound inhibited growth of DNA repair-deficient strains of S. typhimurium and E. coli (Rashid et al., 1984). 4-Chloro-2-methylaniline induced DNA damage in Chinese hamster lung fibroblasts (Zimmer et al., 1980) and inhibited cell growth and RNA synthesis in Hela cells (Murakami and Fukami, 1974). Positive results have also been reported for inhibition of testicular DNA synthesis in male mice (Seiler, 1977) and for mutations at recessive gene coat color loci in mice (Lang, 1984).

Dietary administration of 4-chloro-2-methylaniline hydrochloride to rats at $\geq$250 ppm and mice at $\geq$2000 ppm for 7 weeks resulted in slight but not

dose-related reductions in body weight gains in rats and mice, and splenomegaly at ≥6500 in rats (NCI, 1978). Chronic dietary administration to rats at ≥1250 ppm resulted in no treatment-related effects. Female mice at ≥1250 ppm and male mice at ≥3750 ppm had dose-related decreased body weight gains. They also had dose-related increased mortality and hemosiderosis in the kidney, which were secondary to tumor development.

Since chronic dietary administration of 4-chloro-2-methylaniline hydrochloride is carcinogenic to mice (Weisburger et al., 1978; NCI, 1978), it is appropriate to derive a q_1^*. Male and female mice administered 4-chloro-2-methylaniline hydrochloride in the diet for 18 months and observed for 3 months more had increased vascular hemangiosarcoma and hemangioma incidences relative to simultaneous controls and pooled controls (Weisburger et al., 1978). Males were treated at 750 and 1500 ppm. These concentrations correspond to average intakes of 83.6 and 167.1 mg/kg/day using 0.13 kg food/kg body weight/day as the standard food consumption estimate for mice (U.S. EPA, 1986c) and multiplying by 18 months/21 months. Female mice were fed 2000 or 4000 ppm of 4-chloro-2-methylaniline hydrochloride, which correspond to 222.9 or 445.7 mg/kg/day, respectively, using the standard food consumption estimate and expanding the dose. The unadjusted q_1^* for each sex was calculated relative to each control group using the computerized multistage model developed by Howe and Crump (1982) (Tables 8-1 and 8-2). Tumor incidence in the high-dose female mice (12/16) declined below the incidence (18/19) in the low-dose mice (see Table 5-2) yielding a poor agreement with the multistage model. The highest risk estimate was obtained by extrapolating from the low dose level tumor incidence. Accordingly, the high dose level for female mice was dropped during the calculation of the q_1^*s. The unadjusted q_1^*s were corrected by the cube root of the ratio of the

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: 4-chloro-2-methylaniline hydrochloride

Reference: Weisburger et al., 1978

Species/Strain/sex: mouse, CD-1, male

Route/vehicle: oral, diet

le = 18 months

Le = 21 months

L = 24 months

bw = 0.03 kg (assumed)

Tumor type and site: vascular hemangiosarcomas and hemangiomas

Experimental Doses or Exposure (mg/kg)	Transformed Animal Dose (mg/kg/day)	Incidence No. Responding/No. Tested
0 (simultaneous controls)	0	0/14
0 (pooled controls)	0	5/99
750	83.6	12/20
1500	167.1	13/20

Unadjusted q_1^* = 1.0616×10^{-2} $(mg/kg/day)^{-1}$ (pooled) and 1.1077×10^{-2} $(mg/kg/day)^{-1}$ (simultaneous)

Human q_1^* = 2.1018×10^{-1} $(mg/kg/day)^{-1}$ (pooled) and 2.1931×10^{-1} $(mg/kg/day)^{-1}$ (simultaneous)

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: 4-chloro-2-methylaniline hydrochloride

Reference: Weisburger et al., 1978

Species/Strain/sex: mouse, CD-1, female

Route/vehicle: oral, diet

le = 18 months

Le = 21 months

L = 24 months

bw: 0.03 kg (assumed)

Tumor type and site: vascular hemangiosarcomas and hemangiomas

Experimental Doses or Exposure (mg/kg)	Transformed Animal Dose (mg/kg/day)	Incidence No. Responding/No. Tested
0 (simultaneous controls)	0	0/15
0 (pooled controls)	0	9/102
2000	222.9	18/19
4000	445.7	12/16

Unadjusted q_1^* = 2.277×10^{-2} $(mg/kg/day)^{-1}$ (pooled) and 2.3183×10^{-2} $(mg/kg/day)^{-1}$ (simultaneous)†

Human q_1^* = 4.508×10^{-1} $(mg/kg/day)^{-1}$ (pooled) and 4.5899×10^{-1} $(mg/kg/day)^{-1}$ (simultaneous)†

†The q_1^*s were calculated without the high dose data because when the high-dose group was used, the data did not fit the model.

reference human body weight (70 kg) to the assumed body weight of mice (0.03 kg). Since the length of the experiment (Le) was less than the lifespan of the animal (L), a further correction of $(L/Le)^3$ was applied.

Similar procedures were used to calculate human q_1^*s from tumor data in male and female mice fed 4-chloro-2-methylaniline hydrochloride for 99 weeks (NCI, 1978). The males had incidences of hemangiosarcomas and hemangiomas of 0/20, 6/50 and 41/50 following exposure to 0, 3750 or 15,000 ppm. These concentrations correspond to average intakes of 0, 487.5 and 1950 mg/kg/day of the compound using a standard food consumption estimate for mice of 0.13 kg food/kg body weight/day (U.S. EPA, 1986c). The female mice also developed hemangiosarcomas and hemangiomas with incidences of 1/18, 44/49 and 39/50 for experimental concentrations of 0, 1250 and 5000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet. Using the standard food consumption estimates, the concentrations correspond to average intakes of 0, 162.5 and 650 mg/kg/day. Since the length of the exposure and length of the experiment were the same, there was no need to correct by a factor of le/Le. Because the weights of the mice in different treatment groups varied, each dose was transformed to the equivalent human dose before calculating the q_1^* by multiplying the transformed experimental dose by the cube root of the ratio of the mean mouse body weight to the reference human body weight (70 kg). The animal body weights were taken from data presented in the NCI (1978) report. The dose was further corrected by $(Le/L)^3$, since the length of the experiment was less than the lifespan of the animal. From these data, human q_1^*s of 4.71×10^{-3} and 2.7×10^{-1} $(mg/kg/day)^{-1}$ were calculated directly using the computerized multistage model by Howe and Crump (1982) (Tables 8-3 and 8-4). Table 8-5 summarizes the q_1^*s calculated above for 4-chloro-2-methylaniline hydrochloride. The highest q_1^*

TABLE 8-3

Cancer Data Sheet for Derivation of q_1^*

Compound: 4-chloro-2-methylaniline hydrochloride

Reference: NCI, 1978

Species/Strain/sex: mouse, B6C3F1, male

Route/vehicle: oral, diet

le = 99 weeks

Le = 99 weeks

L = 104 weeks

bw (measured): 0.047 kg controls; 0.043 kg low dose; 0.040 kg high dose

Tumor type and site: hemangiosarcoma and hemangioma, vascular system

Experimental Doses or Exposure		Transformed Animal Dose (mg/kg/day)	Incidence No. Responding/No. Tested
(ppm)	(mg/kg/day)		
0	0	0	0/20
3,750	487.5	35.7	6/50
15,000	1950.0	139.6	41/50

Unadjusted q_1^* from study = not calculated (see text)

Human $q_1^* = 4.73207 \times 10^{-3}$ $(mg/kg/day)^{-1}$

TABLE 8-4

Cancer Data Sheet for Derivation of q_1^*

Compound: 4-chloro-2-methylaniline hydrochloride

Reference: NCI, 1978

Species/Strain/sex: mouse, B6C3F1, female

Route/vehicle: oral, diet

le = 99 weeks (controls and low dose); 92 weeks (high dose)

Le = 99 weeks (controls and low dose); 92 weeks (high dose)

L = 104 weeks

bw (measured): 0.05 kg controls; 0.038 kg low dose; 0.027 high dose

Tumor type and site: hemangiosarcoma and hemangioma, vascular system

Experimental Doses or Exposure		Equivalent Human Dose (mg/kg/day)	Incidence No. Responding/No. Tested
(ppm)	(mg/kg/day)		
0	0	0	1/18
1250	162.5	11.4	44/49
5000	650.0	32.8	39/50

Unadjusted q_1^* from study = not calculated (see text)

Human $q_1^* = 2.6645 \times 10^{-1}$ (mg/kg/day)$^{-1}$†

†The q_1^* was calculated without the high dose data because when the high dose was included, the data did not fit the model.

TABLE 8-5

Summary of Calculated Human q_1^*s for
4-Chloro-2-methylaniline Hydrochloride in the Mouse

Strain	Sex	Human q_1^* $(mg/kg/day)^{-1}$	Reference
CD-1	male	2.1×10^{-1} (pooled controls)	Weisburger et al., 1978
		2.2×10^{-1} (simultaneous controls)	
CD-1	female	4.5×10^{-1} (pooled controls)	Weisburger et al., 1978
		4.6×10^{-1} (simultaneous controls)	
B6C3F1	male	4.7×10^{-3}	NCI, 1978
B6C3F1	female	2.7×10^{-1}	NCI, 1978

of 4.6×10^{-1} $(mg/kg/day)^{-1}$ is for the incidence of hemangiosarcomas and hemangiomas in female mice compared with simultaneous controls in the Weisburger et al. (1978) study. The use of simultaneous controls instead of pooled controls does not significantly affect the estimate. This estimate is corroborated by similar estimates (within a factor of 2 or 3) in male CD-1 mice and in female B6C3F1 mice. This q_1^* is recommended for estimating the increased lifetime risk of cancer for human exposure to 4-chloro-2-methylaniline hydrochloride. The water concentrations of 4-chloro-2-methylaniline hydrochloride associated with risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 7.6×10^{-4}, 7.6×10^{-5} and 7.6×10^{-6} mg/ℓ, respectively.

Since no carcinogenicity data were available, a q_1^* for 4-chloro-2-methylaniline can be derived by multiplying the q_1^* for 4-chloro-2-methylaniline hydrochloride by the ratio of the molecular weight of 4-chloro-2-methylaniline hydrochloride (178.1) to the molecular weight of 4-chloro-2-methylaniline (141.6). Thus, 4.6×10^{-1} $(mg/kg/day)^{-1}$ x 178.1/141.6 = 5.8×10^{-1} $(mg/kg/day)^{-1}$. The q_1^* of 5.8×10^{-1} $(mg/kg/day)^{-1}$ is recommended for estimating the increased lifetime risk of cancer for human exposure to 4-chloro-2-methylaniline. The water concentrations associated with risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 6.0×10^{-4}, 6.0×10^{-5} and 6.0×10^{-7}, respectively.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Information regarding the nonneoplastic effects of subchronic and chronic exposure to 4-chloro-2-methylaniline hydrochloride was provided in the NCI (1978) cancer bioassay. The toxic effects in this study are discussed in Section 5.5. and are summarized in Table 9-1. Transformed doses were calculated by multiplying the dietary concentrations by the food factor of 0.05 for rats and 0.13 for mice. Equivalent human doses were calculated by multiplying the transformed dose by the cube root of the animal body weight to the reference human body weight (70 kg). In the preliminary 7-week study, there was a slight decrease in body weight in the male Fischer 344 rats at dietary concentrations $\geq$250 ppm of 4-chloro-2-methylaniline hydrochloride, but the decrease was not dose-related. In the same study, female rats showed a dose-related severe decrease in body weight at doses $\geq$6200 ppm. Splenomegaly was noted in the males at 6500 ppm 4-chloro-2-methylaniline hydrochloride in the diet for 7 weeks. Mortality was 100% in the females at 50,000 ppm. Male B6C3F1 mice showed a decrease in body weight following administration of 15,000 ppm of 4-chloro-2-methylaniline hydrochloride in the diet during the 7-week subchronic study. The female mice had decreased body weight at doses of 20,000 ppm. Because of the short-term nature of the subchronic study (7 weeks), it is not appropriate to consider it for the chronic toxicity RQ.

In the chronic bioassay (NCI, 1978), male and female rats had decreased body weight gains at 5000 ppm 4-chloro-2-methylaniline hydrochloride in the diet for 107 weeks. Mean body weights of mice showed a dose-related decrease at $\geq$1250 ppm for females and $\geq$3750 ppm for males. Survival of female mice receiving 1250 ppm and male mice receiving 15,000 ppm was

TABLE 9-1

Toxicity Summary for 4-Chloro-2-methylaniline Hydrochloride Administered in the Diet (purity >99%)[a]

Species/ Strain	Sex	Average No. at Start	Vehicle/ Weight (kg)	Dose/Exposure	Transformed Animal Dose (mg/kg/day)	Equivalent Human Dose (mg/kg/day)	Response
Rat/F344	M	5	0.35[b]	6500 ppm in feed for 7 weeks	325.0	55.6	Splenomegaly
	F	5	0.35[b]	6200 ppm in feed for 7 weeks	310.0	53.0	Dose-related severe decreased body weight gain
	F	5	0.35[b]	50,000 ppm in feed for 7 weeks	2500.0	427.5	Mortality
	M/F	5/5	0.35[b]	10,000 ppm in feed for 7 weeks	500.0	85.5	Splenomegaly; increased bone marrow cellularity
Mouse/ B6C3F1	M	5	0.03[b]	15,00 ppm in feed for 7 weeks	520.0	147.0	Decreased body weight
	F	5	0.03[b]	20,000 ppm in feed for 7 weeks	1950.0	196.0	Decreased body weight
Rat/F344	M/F	50/50	0.375 (M) 0.210 (F)	5000 ppm in feed for 107 weeks	250.0	43.7 (M) 36.1 (F)	Decreased body weight
Mouse/ B6C3F1	M	50	0.043	3750 ppm in feed fr 99 weeks	487.5	41.4	Decreased body weight; hemosiderin deposits and splenomegaly secondary to tumor development
	M	50	0.040	15,000 ppm in feed for 99 weeks	1950.0	161.8	Decreased survival due to fatal tumors; decreased body weight
	F	50	0.038	1250 ppm in feed for 99 weeks	162.5	13.3	Decreased survival; renal tubular hemosiderin deposits; splenomegaly all secondary to tumor development; decreased body weight gain

[a]Source: NCI, 1978

[b]Assumed

NR = Not reported

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decreased relative to controls; this was attributed to hemorrhage in the peritoneal cavity after development of tumors. Similarly treated mice had hemosiderosis in the kidney, probably secondary to the tumors, hemorrhage and splenomegaly, which was attributed to extramedullary hematopoiesis in response to the hemorrhage. Because these effects were secondary to tumor development, they are not considered in the derivation of the RQ. Therefore, the only effect useful for RQ derivation is decreased body weight gain. The lowest equivalent dose at which body weight gain was decreased in the chronic study is 13.3 mg/kg/day (female mice at 1250 ppm). Multiplying 13.3 mg/kg/day by 70 kg yields an MED of 931 mg/day, which corresponds to an RV_d of 1.0 (Table 9-2). The RV_e for reduced body weight gain is 4. Multiplying the RV_d by the RV_e yields a CS of 4, which corresponds to an RQ of 5000 (Table 9-3) for 4-chloro-2-methylaniline hydrochloride.

Multiplying the MED of 931 mg/day for 4-chloro-2-methylaniline hydrochloride by the ratio of the molecular weights of 4-chloro-2-methylaniline to the hydrochloride (141.6/178.1 = 0.795059) yields an MED of 740 mg/day for 4-chloro-2-methylaniline. The MED corresponds to an RV_d of 1.2, which when multiplied by the RV_e of 4 yields a CS of 4.8, which also corresponds to an RQ of 5000 (Table 9-4).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

The information regarding the carcinogenicity of 4-chloro-2-methylaniline hydrochloride was discussed in Section 5.1. Chronic dietary exposure to 4-chloro-2-methylaniline hydrochloride resulted in significantly increased incidences of hemangiosarcomas and hemangiomas in both sexes of two strains of mice in two different experiments (Weisburger et al., 1978; NCI, 1978). IARC (1983), on the basis of these studies, concluded that

TABLE 9-2

Oral Composite Scores for 4-Chloro-2-methylaniline Hydrochloride in the Mouse*

Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ
162.5	931	1	decreased body weight	4	4	5000

*Source: NCI, 1978

TABLE 9-3

4-Chloro-2-methylaniline Hydrochloride

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	913 mg/day
Effect:	decreased body weight gain
Reference:	NCI, 1978
RV_d:	1
RV_e:	4
Composite Score:	4
RQ:	5000

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*Equivalent human dose

TABLE 9-4

4-Chloro-2-methylaniline

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose[a,b]:	740 mg/day
Effect:	decreased body weight gain
Reference:	NCI, 1978
RV_d:	1.2
RV_e:	4
Composite Score:	4.8
RQ:	5000

---

[a]Equivalent human dose

[b]The compound administered was 4-chloro-2-methylaniline hydrochloride

there is sufficient evidence that 4-chloro-2-methylaniline and 4-chloro-2-methylaniline hydrochloride are carcinogenic in animals. There were no case reports or epidemiological studies regarding the carcinogenicity of 4-chloro-2-methylaniline or its hydrochloride in humans. Therefore, these chemicals are classified as IARC 2B and EPA Group B2 chemicals, that is, probable human carcinogens (U.S. EPA, 1986d).

As discussed in Chapter 8, q_1^*s for these chemicals were derived using the data for hemangiosarcoma/hemangioma in female mice in the study by Weisburger et al. (1978). Potency (F) factors for carcinogenicity can also be derived from the same data (Table 9-5). The transformed doses (222.9, 445.7 mg/kg/day) were calculated from dietary concentrations adjusted for differences in duration of treatment (le) and duration of the study (Le) by multiplying the animal dose by le/Le (18/months/21 months) and the estimated food factor for mice (0.13 kg food/kg body weight/day). The unadjusted F factor for 4-chloro-2-methylaniline hydrochloride of 1.2537613×10^{-1} $(mg/kg/day)^{-1}$ was calculated using the computerized multistage model developed by Howe and Crump (1982). The F factor of 2.5 $(mg/kg/day)^{-1}$ was calculated by multiplying the unadjusted $1/ED_{10}$ by the cube root of the ratio of human body weight (70 kg) to the reference mouse body weight (0.03 kg) and by the cube of the ratio of the lifespan to the duration of the study.

An F factor of 3.1 $(mg/kg/day)^{-1}$ for 4-chloro-2-methylaniline can be derived by multiplying the F factor for 4-chloro-2-methylaniline hydrochloride by the ratio of the molecular weight of 4-chloro-2-methylaniline hydrochloride to 4-chloro-2-methylaniline (178.1/141.6). Because the F-factors are >1, these chemicals are placed in Potency Group 2. Potency Group 2 chemicals with EPA Group B2 classification have a MEDIUM hazard ranking under CERCLA.

TABLE 9-5

Derivation of Potency Factor (F)
for 4-Chloro-2-methylaniline Hydrochloride

Reference:	Weisburger et al., 1978		
Exposure Route:	oral		
Species:	mouse		
Strain:	CD-1		
Sex:	female		
Vehicle or Physical State:	diet		
Body Weight:	0.03 kg (assumed)		
Duration of Treatment:	18 months		
Duration of Study:	21 months		
Lifespan of Animal:	24 months		
Target Organ:	vascular		
Tumor Type:	hemangiosarcomas and hemangiomas		
Experimental Doses/Exposure (mg/kg):	0 (simultaneous controls)	2000	4000
Transformed Doses (mg/kg/day):	0	222.9	445.7
Tumor Incidence:	0/15	18/19	12/16
Unadjusted $1/ED_{10}$:	1.2537613×10^{-1} (mg/kg/day)$^{-1}$*		
F factor:	2.4822729 (mg/kg/day)$^{-1}$*		

*These values were calculated using the low-dose and the control group only because when the high-dose group was included, the data did not fit the model.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

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Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

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In addition, the following document was consulted during the preparation of this HEEP:

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